Attorney Docket No. NEX90/C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	PIETRAS *ET AL.*	EXAMINER: VIVLEMORE, T.
SERIAL NO.:	10/791,367	ART UNIT: 1635
FILED:	MARCH 2, 2004	CONFIRMATION NO: 9750
TITLE:	METHODS AND COMPOSITIONS FOR TREATMENT OF TUMORS USING NUCLEIC ACID LIGANDS TO PLATELET-DERIVED GROWTH FACTOR	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION

Dear Sir:

An Office Action was mailed in the above-captioned application on March 8, 2006. In such Office Action pending claims 1-10 were pending. Claims 1-10 were rejected. This document is submitted in response to said Office Action.

Amendments to the Specification begin of page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 4 of this paper.

Remarks/Arguments begin on page 8 of this paper.

Amendments to the Specification:

Please replace paragraph 5, page 6 with the following amended paragraph:

Figure 5 illustrates graphically the increased uptake of the chemotherapeutic agent ~~taxol~~ TAXOL® (paclitaxel) upon pretreatment of KAT-4 tumors with PDGF aptamers.

Please replace paragraph 1, page 9 with the following amended paragraph:

A "**cytotoxic agent**" is any substance used to destroy tumor cells. The method of this invention can be used with any systemically administrated cytotoxic agent including, but not limited to, Bleomycin, Cisplatin, and Pt analogues; Carboplatin and Iproplatin, Cyclophosphamide, Daunorubicin, Doxofluoridine, Doxorubicin, Etoposide, Epirubicin, 5-Flurouracil, ~~Gemzar~~ GEMZAR® (Gemcitabine HCL), Ifosfamide, Melphalan, Methotrexate, Mithramycin, Mitomycin C, Mitoxanthrone, Streptozotocin, ~~Taxol~~ TAXOL® (paclitaxel) and ~~Taxotere~~ TAXOTERE® (docetaxel), Vincristine, Vinblastine, Vindesine, Vinorelbine, Topotecan and CPT-11.

Please replace paragraph 1, page 14 with the following amended paragraph:

As noted above, the cytotoxic agent can be any substance used in the prevention, diagnosis, alleviation, treatment or cure of disease. More specifically, the cytotoxic agent can be selected from any systemically administrated agent including, but not limited to, Bleomycin, Cisplatin, and Pt analogues; Carboplatin and Iproplatin, Cyclophosphamide, Daunorubicin, Doxofluoridine, Doxorubicin, Etoposide, Epirubicin, 5-Flurouracil, ~~Gemzar~~ GEMZAR® (Gemcitabine HCL), Ifosfamide, Melphalan, Methotrexate, Mithramycin, Mitomycin C, Mitoxanthrone, Streptozotocin, ~~Taxol~~ TAXOL® (paclitaxel) and ~~Taxotere~~ TAXOTERE® (docetaxel), Vincristine, Vinblastine, Vindesine, Vinorelbine, Topotecan and CPT-11.

Please replace paragraph 3, page 16 with the following amended paragraph:

Prompted by these findings, the effects of treatment with PDGF aptamer (SEQ ID NO:1) were tested on the KAT-4 tumor model (Examples 4 and 5). Both of these tumor models showed PDGF receptor expression in tumor stroma but not on tumor cells. As can be seen in Figures 4

and 5 treatment with PDGF aptamers lowers IFP in KAT-4 tumors and increases the uptake of ~~taxol~~ TAXOL® (paclitaxel).

Please replace heading 1, page 19 with the following amended heading:
Example 5. Treatment of KAT-4 tumors with a PDGF Inhibitor in Combination with the Cytotoxic Agent ~~Taxol~~ TAXOL® (paclitaxel)

Please replace paragraph 1, page 19 with the following amended paragraph:

SCID-mice bearing subcutaneous KAT-4 tumors (human, anaplastic thyroid carcinoma) were pre-treated for 4 consecutive days with 12 mg x kg^{-1} x day $^{-1}$ SELEX aptamers (i.p. injections, three times daily). [^{3}H]~~taxol~~ TAXOL® (paclitaxel) was injected s.c at a site distant from the tumor and in a mix of 5 mg x kg^{-1} unlabelled ~~taxol~~ TAXOL® (paclitaxel). Eight or 24 hours following injection of radiolabelled drug, blood was sampled, animals were sacrificed and tumors and 4 other tissues were excised. Subsequently, tissues were weighed and homogenized in a RIPA lysis buffer and the amount radioactivity in each sample was determined in a scintillation counter. Tumor uptake of ~~taxol~~ TAXOL® (paclitaxel) was expressed as cpm/g tumor tissue divided by cpm/ml blood. The results are set forth in Figure 5. * $p<0.05$, Student's t-test.

In the Claims

This listing of the claims replaces all prior versions and listings of the claims.

1. (original) A method for treating tumors comprising:

a) pre-treating a host having a tumor by administering a therapeutically effective dose of a platelet-derived growth factor (PDGF) aptamer for a predetermined number of days; and

b) subsequently administering a therapeutically effective dose of a cytotoxic agent to said host.

2. (original) The method of claim 1 wherein in step b) said cytotoxic agent is administered in combination with said PDGF aptamer.

3. (original) The method of claim 1 wherein said PDGF aptamer is identified according to a method comprising:

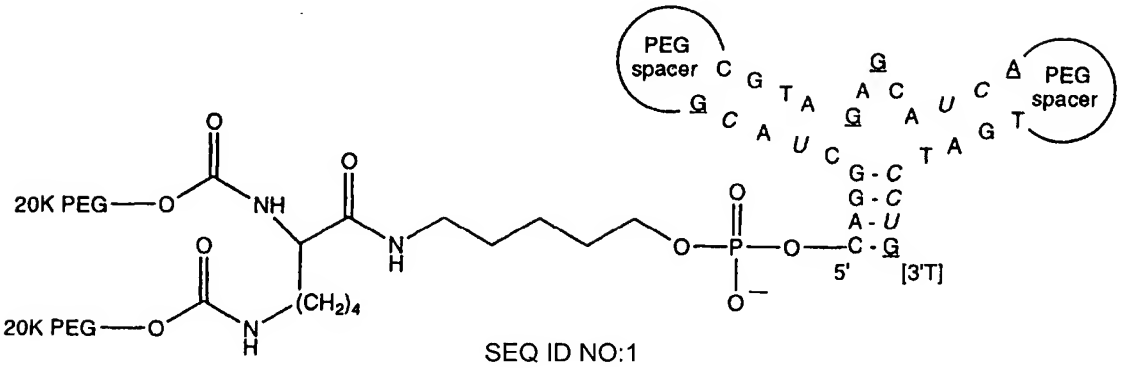
a) preparing a candidate mixture of nucleic acids;

b) contacting the candidate mixture of nucleic acids with PDGF, wherein nucleic acids having an increased affinity to PDGF relative to the candidate mixture may be partitioned from the remainder of the candidate mixture;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture; and

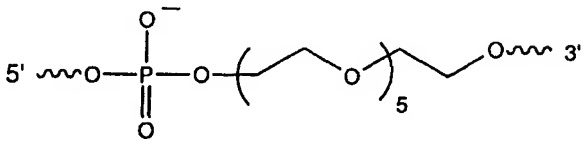
d) amplifying the increased affinity nucleic acids to yield a mixture of nucleic acids enriched for nucleic acids with relatively higher affinity and specificity for binding to PDGF, whereby a nucleic acid ligand of PDGF may be identified.

4. (original) The method of claim 1 wherein said PDGF aptamer is:



SEQ ID NO:1

wherein: U at positions 6, 20 and 30 is 2'-fluoro-2'-deoxyuridine.
C at positions 8, 21, 28, and 29 is 2'-fluoro-2'-deoxycytidine.
G at positions 9, 15, 17, and 31 is 2'-O-Methyl-2'-deoxyguanosine.
A at position 22 is 2'-O-Methyl-2'-deoxyadenosine; and

wherein PEG spacer = 

5. (currently amended) The method of claim 1 wherein said cytotoxic agent is selected from the group consisting of Bleomycin, Cisplatin, and Pt analogues; Carboplatin and Iproplatin, Cyclophosphamide, Daunorubicin, Doxofluoridine, Doxorubicin, Etoposide, Epirubicin, 5-Flurouracil, ~~Gemzar~~ Gemcitabine HCL, Ifosfamide, Melphalan, Methotrexate, Mithramycin, Mitomycin C, Mitoxanthrone, Streptozotocin, ~~Taxol~~ paclitaxel and ~~Taxotere~~ docetaxel, Vincristine, Vinblastine, Vindesine, Vinorelbine, Topotecan and CPT-11.

6. (original) A method for increasing the uptake of cytotoxic agents into a tumor comprising:

a) pre-treating a host having a tumor by administering a therapeutically effective dose of a platelet-derived growth factor (PDGF) aptamer for a predetermined number of days; and

b) subsequently administering a therapeutically effective dose of a cytotoxic agent to said host.

7. (original) The method of claim 6 wherein in step b) said cytotoxic agent is administered in combination with said PDGF aptamer.

8. (original) The method of claim 6 wherein said PDGF aptamer is identified according to a method comprising:

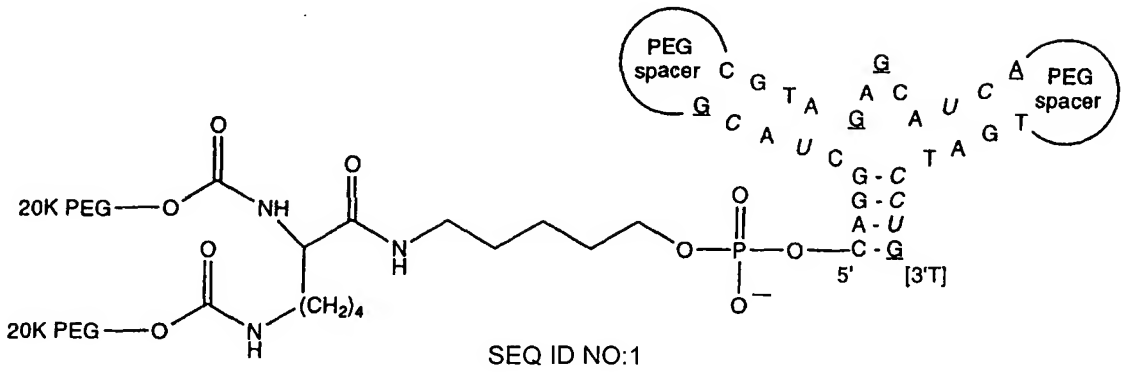
a) preparing a candidate mixture of nucleic acids;

b) contacting the candidate mixture of nucleic acids with PDGF, wherein nucleic acids having an increased affinity to PDGF relative to the candidate mixture may be partitioned from the remainder of the candidate mixture;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture; and

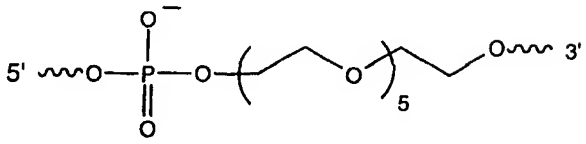
d) amplifying the increased affinity nucleic acids to yield a mixture of nucleic acids enriched for nucleic acids with relatively higher affinity and specificity for binding to PDGF, whereby a nucleic acid ligand of PDGF may be identified.

9. (original) The method of claim 6 wherein said PDGF aptamer is:



SEQ ID NO:1

wherein: U at positions 6, 20 and 30 is 2'-fluoro-2'-deoxyuridine.
C at positions 8, 21, 28, and 29 is 2'-fluoro-2'-deoxycytidine.
G at positions 9, 15, 17, and 31 is 2'-O-Methyl-2'-deoxyguanosine.
A at position 22 is 2'-O-Methyl-2'-deoxyadenosine; and

wherein PEG spacer = 

10. (currently amended) The method of claim 6 wherein said cytotoxic agent is selected from the group consisting of Bleomycin, Cisplatin, and Pt analogues; Carboplatin and Iproplatin, Cyclophosphamide, Daunorubicin, Doxofluoridine, Doxorubicin, Etoposide, Epirubicin, 5-Flurouracil, ~~Gemzar~~ Gemcitabine HCL, Ifosfamide, Melphalan, Methotrexate, Mithramycin, Mitomycin C, Mitoxanthrone, Streptozotocin, ~~Taxol~~ paclitaxel and ~~Taxotere~~ docetaxel, Vincristine, Vinblastine, Vindesine, Vinorelbine, Topotecan and CPT-11.

11.- 14. Cancel.

REMARKS/ARGUMENTS

In an Office Action dated March 8, 2006, claims 1-10 are pending in the application. Claims 1-10 were rejected. This document is submitted in response to said Office Action.

Specification

The Examiner has objected to the specification with regard to the use of trademarks GEMZAR®, TAXOL® and TAXOTERE®. The specification has been amended to comport with the Examiner's instructions.

Claim Rejections Under 35 U.S.C. §112

Claims 5 and 10 have been rejected as non compliant with the requirements of 35 U.S.C. §112, second paragraph, in that a trademark or trade name cannot be used in a claim as a limitation to identify or describe a particular material or product. Applicants have amended claims 5 and 10 to recite the generic names of the trademarks GEMZAR®, TAXOL® and TAXOTERE®.

Double Patenting Rejection

The Examiner has rejected claims 1-10 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 8-11 of U.S. Patent No. 6,699,843. An obviousness-type double patenting rejection is appropriate when a claim merely defines an obvious variation of an invention claimed in a patent. M.P.E.P. § 804(II)(B)(1). A double-patenting rejection must rely on a comparison with the claims in an issued or to be issued patent. M.P.E.P. § 804(III).

The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are directed to methods of treating tumors and increasing cellular uptake of a cytotoxic agent by administering a PDGF aptamer and a cytotoxic agent. The instant claims specify that the administration of the aptamer and the cytotoxic agent is separated by a number of days. The Examiner reasons that the instant

claims are an obvious variation of the patented claims because the specific embodiment of sequential administration now claimed was actually exemplified in the patent.

Submitted herewith is a Terminal Disclaimer to obviate a double patenting rejection over a prior patent. It is believed that that the Terminal Disclaimer is sufficient to overcome the double-patenting rejection. Reconsideration is respectfully requested.

Closing Remarks

Applicants believe that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: 6/7/06

Katherine Lobel-Rice, #58,079
Swanson & Bratschun, L.L.C.
1745 Shea Center Drive, Suite 330
Highlands Ranch, Colorado 80129
Telephone: (303) 268-0066
Facsimile: (303) 268-0065

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